

An Observational, Non-interventional, Multicenter, Multinational Registry of Patients With Atypical Hemolytic Uremic Syndrome: Methodology

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INTRODUCTION

Atypical Hemolytic Uremic Syndrome: Background

- Atypical hemolytic uremic syndrome (aHUS) is a genetic, progressive, life-threatening disease mostly resulting from chronic, uncontrolled complement activation. It is characterized by systemic thrombotic microangiopathy (TMA) leading to renal and other end-organ damage
- Plasma exchange and infusion (PE/PI) has historically been used to manage aHUS¹; however, evidence suggests that PE/PI offers no significant benefit over simple supportive therapy^{2,3}
- Eculizumab (Soliris®; Alexion Pharmaceuticals, Inc., Cheshire, CT), a terminal complement inhibitor, is a humanized monoclonal antibody that binds with high affinity to the human C5 complement protein, blocking the generation of pro-inflammatory C5a and C5b-9⁴
- Eculizumab is the first approved treatment for aHUS in pediatric and adult patients⁴⁻⁷
- A single, global aHUS patient registry can maximize both physician and patient participation to best capture information on disease, safety, and efficacy data in a population with a very rare disease
- The global aHUS patient registry (ClinicalTrials.gov identifier: NCT01522183) was initiated in April 2012 to prospectively capture postmarketing effectiveness and safety data on patients treated with eculizumab; the registry will record information on the progression of disease in all aHUS patients (whether treated with eculizumab or with other disease management strategies)
- Furthermore, the registry fulfills postmarketing regulatory requirements by providing follow-up on the aHUS indication for eculizumab, and exemplifies the need for and benefit of successful partnering between sponsors and academia

OBJECTIVE

- To report patient characteristics and describe important milestones achieved by patients enrolled in the aHUS registry from its inception (April 2012) through 1 year (April 1, 2013)

METHODS

Patient Eligibility Criteria

- Inclusion criteria
 - Male or female patients of any age who have been diagnosed clinically with aHUS
 - With or without an identified complement regulatory factor genetic abnormality or anti-complement factor antibody (if tested)
 - ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif; C-terminal carboxy-terminal) >5%, if performed
 - Written informed consent from a patient or parent/legal guardian (if applicable as determined by the central Institutional Review Boards/Independent Ethics Committees)
- Exclusion criteria
 - HUS due only to Shiga toxin-producing *Escherichia coli*

Primary Outcome Measures

- Proportion of patients who experience pre-specified events
- Collection and evaluation of safety and efficacy data specific to the use of eculizumab in patients with aHUS
- Time to first and subsequent occurrence of pre-specified events
- Assessment of the long-term manifestations of TMA complications of aHUS; other clinical outcomes, including morbidity and mortality in patients with aHUS receiving eculizumab treatment or treated with other disease-management approaches

Data Collection

- Data are collected at study enrollment and every 6 months thereafter and include the following:
 - Demographics
 - Medical and disease history
 - Symptomology
 - Targeted laboratory results (including genetic results)
 - TMA complications
 - Associated treatments and concomitant medications
 - Clinical and patient-reported outcomes
 - Safety of eculizumab and other aHUS treatments
- To follow each patient and assess long-term outcomes for a minimum of 5 years, information from patient medical records is entered via a secure web portal and maintained anonymously

Registry Support

- The registry is supported by Alexion Pharmaceuticals, Inc., with governance by an independent scientific advisory board (SAB) and national coordinators representing each participating country
- Some key responsibilities of the SAB are to:
 - Provide scientific advice on aHUS registry-related matters
 - Propose, discuss, and evaluate program objectives with Alexion
 - Review and provide guidance on future amendments to the protocol, data variables to be collected, and case report refinements (all as appropriate)
 - Advise on analyses and scientific questions of interest
 - Review and provide feedback on publication goals and logistics
 - Contribute to the development of the publication plan
 - Establish and follow protocols for the review and approval of external requests for analyses and publications from individual investigators or national coordinators
 - Advise, counsel, and guide individuals on publications that utilize aHUS registry data and resources and/or use the aHUS registry name
 - Review publication drafts before submission to journals or public release

Inclusion for the Current Analysis

- All enrolled patients with the following data were included in this analysis:
 - Ever treated with eculizumab or never treated with eculizumab
 - Registry enrollment date, date of birth, and sex must be available
 - For treated patients, date of first eculizumab treatment (if treated) must also be available

RESULTS

Patient Characteristics in Global aHUS Patient Registry

- Tables 1–4** provide information on demographics, aHUS diagnosis, baseline clinical characteristics, and eculizumab treatment characteristics

Countries Enrolling Patients Into aHUS Patient Registry (as of April 1, 2013)

- Australia (n=7)
- Austria (n=4)
- Denmark (n=1)
- Germany (n=2)
- Israel (n=1)
- Spain (n=8)
- United Kingdom (n=5)
- United States (n=25)

Breakdown of Enrolling Sites: Specialist Type

- Nephrologists (84%)
- Hematologists (16%)

Breakdown of Enrolling Sites: Adult– Versus Pediatric–centric

- Pediatric–centric sites (52%)
- Adult–centric sites (47%)

Table 1. Patient Demographics in Global aHUS Patient Registry (as of April 1, 2013)

	Ever Treated With Eculizumab (n=32)	Never Treated With Eculizumab (n=21)	Total (N=53)
Mean age at registry enrollment (SD), years	38.1 (18.38)	33.0 (15.62)	36.1 (17.36)
Age at registry enrollment, n (%)			
≥2 to <5 years	2 (6.3)	2 (9.5)	4 (7.5)
≥5 to <12 years	1 (3.1)	0 (0.0)	1 (1.9)
≥12 to <18 years	0 (0.0)	1 (4.8)	1 (1.9)
≥18 years	29 (90.6)	18 (85.7)	47 (88.7)
Sex, n (%)			
Female	22 (68.8)	7 (33.3)	29 (54.7)
Male	10 (31.3)	14 (66.7)	24 (45.3)
Race, n (%)			
Black	2 (6.3)	0 (0.0)	2 (3.8)
Caucasian	29 (90.6)	21 (100.0)	50 (94.3)
Latino	1 (3.1)	0 (0.0)	1 (1.9)
Year of registry enrollment, n (%)			
2012	17 (53.1)	4 (19.0)	21 (39.6)
2013	15 (46.9)	17 (81.0)	32 (60.4)

aHUS, atypical hemolytic uremic syndrome; SD, standard deviation.

Table 2. aHUS Diagnosis Characteristics at Registry Entry (as of April 1, 2013)

	Ever Treated With Eculizumab (n=32)	Never Treated With Eculizumab (n=21)	Total (N=53)
Mean age at initial symptoms (SD), years	37.7 (19.84) (n=29)	24.2 (13.63) (n=15)	33.1 (18.94) (n=44)
Mean age at diagnosis (SD), years	39.2 (19.00) (n=28)	25.8 (15.97) (n=15)	34.5 (18.95) (n=43)
Family history of aHUS, n (%)			
N/A	28 (87.5)	15 (71.4)	43 (81.1)
Yes	4 (12.5)	6 (28.6)	10 (18.9)
Any identified complement genetic mutation or auto-antibody, n (%)			
N/A	3 (9.4)	7 (33.3)	10 (18.9)
No	20 (62.5)	7 (33.3)	27 (50.9)
Yes	9 (28.1)	7 (33.3)	16 (30.2)

aHUS, atypical hemolytic uremic syndrome; N/A, not available; SD, standard deviation.

Table 3. Baseline Clinical Characteristics of Patients at Registry Entry (as of April 1, 2013)

	Ever Treated With Eculizumab (n=32)	Never Treated With Eculizumab (n=21)	Total (N=53)
Any prior kidney transplant, n (%)			
Yes	4 (12.5)	1 (4.8)	5 (9.4)
Any prior dialysis, n (%)			
Yes	15 (46.9)	4 (19.0)	19 (35.8)
Any prior plasma exchange/infusion, n (%)			
Yes	17 (53.1)	4 (19.0)	21 (39.6)
Mean baseline eGFR (SD), mL/min/1.73 m ²	10.6 (7.29) (n=7)	86.8 (116.73) (n=2)	27.6 (53.58) (n=9)

eGFR, estimated glomerular filtration rate; SD, standard deviation.

Table 4. Characteristics of Patients Treated With Eculizumab at Registry Entry (as of April 1, 2013)

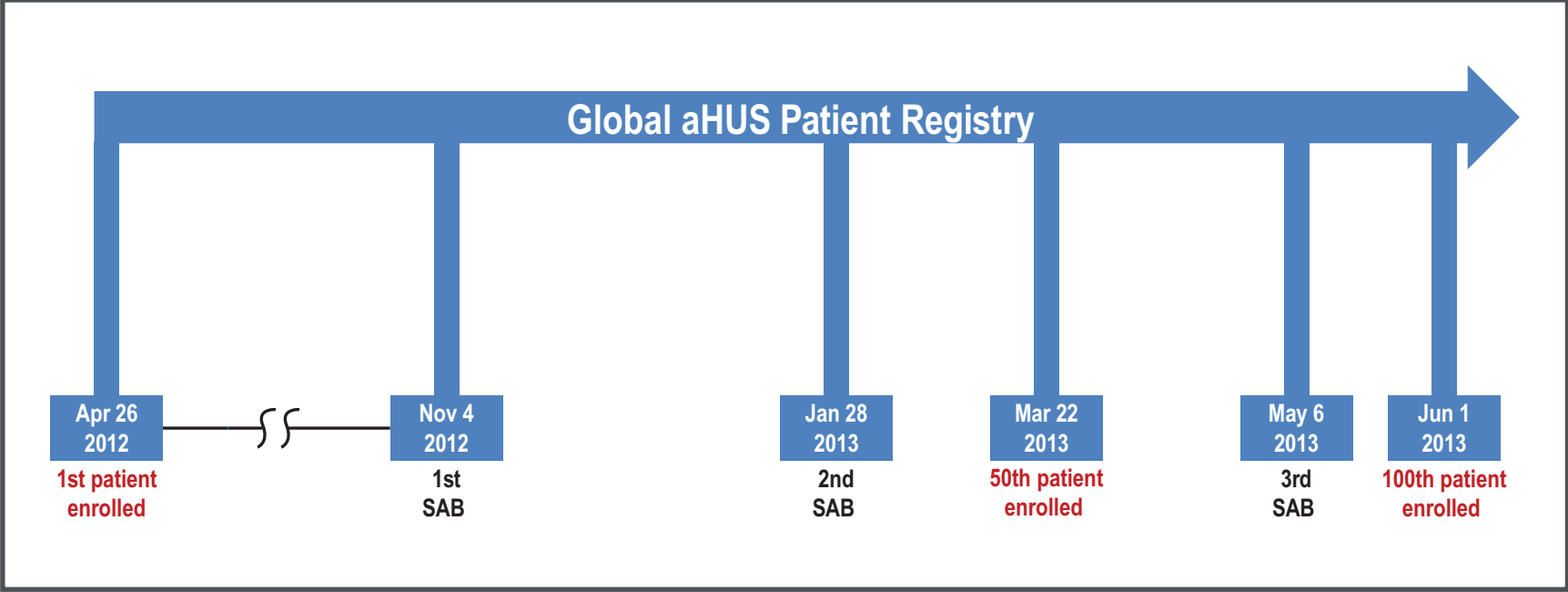
	Ever Treated With Eculizumab (N=32)
Mean age at eculizumab treatment initiation (SD), years	38.1 (18.38) (n=47)
Median dose at initiation of eculizumab (range), mg	900.0 (600–1200)
Mean time on eculizumab (SD), years	0.9 (0.85) (n=31)
Any discontinuation of eculizumab, n (%)	
No	30 (93.8)
Yes	2 (6.3)
Restarted eculizumab (among those who discontinued), n (%)	
No	1 (50.0)
Yes	1 (50.0)

SD, standard deviation.

Milestones Achieved for the Global aHUS Patient Registry

- Figure 1** shows the milestones that have been reached to date since enrollment of the first patient on April 26, 2012

Figure 1. aHUS Patient Registry: a Timeline of Milestones Reached to Date



aHUS, atypical hemolytic uremic syndrome; SAB, scientific advisory board

CONCLUSIONS

- Based on the limited enrollment at this time, reflecting the early stage of the registry, it would be premature to draw scientific conclusions from the data presented in this poster
- The global aHUS patient registry is dedicated to increasing the understanding and awareness of aHUS disease history and progression
- The results of analyses from collected data and outcomes provide an opportunity to optimize care and improve quality of life for aHUS patients
- A single, global aHUS patient registry can maximize both physician and patient participation to best capture information on disease, safety, and efficacy data in a population with a very rare disease
- New clinical sites are encouraged to participate

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